

We claim:

1. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 4, 6, 8, 10, 12, 14, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, and 196, or functional fragment thereof.
2. The butyrylcholinesterase variant of claim 1, having at least a two-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.
3. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 24, 26, 30, 32, 34, 36, 38, 104, 106, 108, 110, 112, 116, 118, 120, 122, 124, 126, 128, 132, 134, 136, 140, and 142, or functional fragment thereof.
4. The butyrylcholinesterase variant of claim 3, having at least a fifty-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.
5. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 36, 108, 110, 112, 122, 124, 134, 178, 180, 182, 186, 188, 190, 192 and 196, or functional fragment thereof.
6. The butyrylcholinesterase variant of claim 5, having at least a one hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.
7. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180, 182, 184, 186, 188, 192 and 196, or functional fragment thereof.

8. The butyrylcholinesterase variant of claim 7, having at least a five hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

9. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180, 182, 184, 188 and 192, or functional fragment thereof.

10. The butyrylcholinesterase variant of claim 9, having at least a six hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

11. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180, 182, 184 and 188, or functional fragment thereof, or functional fragment thereof.

12. The butyrylcholinesterase variant of claim 11, having at least an eight hundred hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

13. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180, 184 and 188, or functional fragment thereof.

14. The butyrylcholinesterase variant of claim 13, having at least a fifteen hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

15. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180 and 188, or functional fragment thereof.

16. The butyrylcholinesterase variant of claim 15, having at least a two thousand-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

17. A butyrylcholinesterase variant comprising the amino acid sequence selected from the group consisting of SEQ ID NOS: 178 and 180, or functional fragment thereof.

18. The butyrylcholinesterase variant of claim 17, having at least a two thousand five hundred-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

19. A butyrylcholinesterase variant comprising the amino acid sequence designated SEQ ID NO: 180, or functional fragment thereof.

20. The butyrylcholinesterase variant of claim 19, having at least a three thousand-fold increase in camptothecin conversion activity compared to butyrylcholinesterase, or functional fragment thereof.

21. The butyrylcholinesterase variant of claim 1, 3, 5, 7, 9, 11, 13, 15, 17 or 19, or functional fragment thereof, further comprising an antibody or antibody fragment.

22. The butyrylcholinesterase variant of claim 21, wherein said antibody or antibody fragment specifically binds the epidermal growth factor receptor (EGFR).

23. The butyrylcholinesterase variant of claim 22, wherein said antibody or antibody fragment comprises an amino acid sequence as shown in SEQ ID NOS: 18 and 20.

24. The butyrylcholinesterase variant of claim 21, wherein said antibody or antibody fragment specifically binds the CD20 cell surface antigen.

25. The butyrylcholinesterase variant of claim 24, wherein said antibody or antibody fragment comprises an amino acid sequence as shown in SEQ ID NOS: 198 and 200.

26. The butyrylcholinesterase variant of claim 25, comprising the sequence shown in Figure 19 and designated SEQ ID NO: 202 .

27. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 178.

28. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 180.

29. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 182.

30. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 184.

31. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 186.

32. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 188.

33. The butyrylcholinesterase variant of claim 5, wherein said amino acid sequence comprises SEQ ID NO: 190.

34. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 192.

35. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 194.

36. The butyrylcholinesterase variant of claim 7, wherein said amino acid sequence comprises SEQ ID NO: 196.

37. A nucleic acid encoding a butyrylcholinesterase variant comprising the nucleic acid sequence selected from SEQ ID NOS: 3, 5, 7, 9, 11, 13, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 163, 165, 167, 169, 171, 173, 175, 177, 179, 181, 183, 185, 187, 189, 191, 193, and 195, or fragment thereof.

38. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 177, or a functional fragment thereof.

39. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 179, or a functional fragment thereof.

40. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 181, or a functional fragment thereof.

41. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 183, or a functional fragment thereof.

42. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 185, or a functional fragment thereof.

43. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 187, or a functional fragment thereof.

44. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 189, or a functional fragment thereof.

45. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 191, or a functional fragment thereof.

46. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 193, or a functional fragment thereof.

47. The nucleic acid of claim 37, wherein said nucleic acid sequence comprises SEQ ID NO: 195, or a functional fragment thereof.

48. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194 and 196, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

49. The method of claim 48, wherein said butyrylcholinesterase variant exhibits a two-fold or greater increase in conversion capability compared to butyrylcholinesterase.

50. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from SEQ ID NOS: 24, 26, 30, 32, 34, 36, 38, 104, 106, 108, 110, 112, 116, 118, 120, 122, 124, 126, 128, 132, 134, 136, 140 and 142, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

51. The method of claim 50, wherein said butyrylcholinesterase variant exhibits a fifty-fold or greater increase in conversion capability compared to butyrylcholinesterase.

52. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 36, 108, 110, 112, 122, 124, 134, 178, 180, 182, 186, 188, 190, 192 and 196, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

53. The method of claim 52, wherein said butyrylcholinesterase variant exhibits a one hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

54. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 178, 180, 182, 184, 186, 188, 192 and 196, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

55. The method of claim 54, wherein said butyrylcholinesterase variant exhibits a five hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

56. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 180, 182, 184, 188 and 192, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

57. The method of claim 56, wherein said butyrylcholinesterase variant exhibits a six hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

58. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 180, 182, 184 and 188, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

59. The method of claim 58, wherein said butyrylcholinesterase variant exhibits a eight hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

60. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 180, 184 and 188, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

61. The method of claim 60, wherein said butyrylcholinesterase variant exhibits a fifteen hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

62. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 178, 180 and 188, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

63. The method of claim 62, wherein said butyrylcholinesterase variant exhibits a two thousand-fold or greater increase in conversion capability compared to butyrylcholinesterase.



64. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 178 and 180, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

65. The method of claim 64, wherein said butyrylcholinesterase variant exhibits a two thousand five hundred-fold or greater increase in conversion capability compared to butyrylcholinesterase.

66. A method of converting a camptothecin derivative to a topoisomerase inhibitor comprising contacting said camptothecin derivative with a butyrylcholinesterase variant comprising an amino acid sequence designated SEQ ID NO: 180, or functional fragment thereof, under conditions that allow conversion of a camptothecin derivative to a topoisomerase inhibitor.

67. The method of claim 66, wherein said butyrylcholinesterase variant exhibits a three thousand-fold or greater increase in conversion capability compared to butyrylcholinesterase.

68. The method of claim 48, 50, 52, 54, 56, 58, 60, 62, 64 or 66, wherein said topoisomerase inhibitor is SN-38.

69. The method of claim 68, wherein said camptothecin derivative is CPT-11.

70. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 178, or a functional fragment thereof.

71. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 180, or a functional fragment thereof.

72. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 182, or a functional fragment thereof.

73. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 184, or a functional fragment thereof.

74. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 186, or a functional fragment thereof.

75. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 188, or a functional fragment thereof.

76. The method of claim 52, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 190, or a functional fragment thereof.

77. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 192, or a functional fragment thereof.

78. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 194, or a functional fragment thereof.

79. The method of claim 54, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 196, or a functional fragment thereof.

80. A method of treating cancer comprising administering to an individual an effective amount of a butyrylcholinesterase variant selected from SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, and 196, or functional fragment thereof, exhibiting increased capability to convert a camptothecin derivative to a topoisomerase inhibitor compared to butyrylcholinesterase.

81. The method of claim 80, wherein said cancer is metastatic colorectal cancer.

82. The method of claim 80, wherein said cancer is ovarian cancer.

83. The method of claim 80, wherein said cancer is lung cancer.

84. The method of claim 80, wherein said cancer is non-Hodgkin's lymphoma.

85. The method of claim 80, wherein said topoisomerase inhibitor is SN-38.

86. The method of claim 80, wherein said camptothecin derivative is CPT-11.

87. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 178, or a functional fragment thereof.

88. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 180, or a functional fragment thereof.

89. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 182, or a functional fragment thereof.

90. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 184, or a functional fragment thereof.

91. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 186, or a functional fragment thereof.

92. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 188, or a functional fragment thereof.

93. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 190, or a functional fragment thereof.

94. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 192, or a functional fragment thereof.

95. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 194, or a functional fragment thereof.

96. The method of claim 80, wherein said butyrylcholinesterase variant comprises the amino acid sequence shown in SEQ ID NO: 196, or a functional fragment thereof.

97. The method of claim 80, wherein said butyrylcholinesterase variant further comprises an antibody or antibody fragment.

98. The method of claim 97, wherein said antibody or antibody fragment specifically binds the epidermal growth factor receptor (EGFR).

99. The method of claim 98, wherein said antibody or antibody fragment comprises an amino acid sequence as shown in SEQ ID NOS: 18 and 20.

100. The method of claim 97, wherein said antibody or antibody fragment specifically binds the CD20 cell surface antigen.

101. The method of claim 100, wherein said antibody or antibody fragment comprises an amino acid sequence as shown in SEQ ID NOS: 198 and 200.

102. The method of claim 97, wherein said butyrylcholinesterase comprises the sequence shown in Figure 19 and designated SEQ ID NO: 202.

103. The method of claim 97, wherein said butyrylcholinesterase variant comprises the amino acid sequence designated as SEQ ID NO: 180, or functional fragment thereof.

104. The method of claim 103, wherein said functional fragment is a L530 truncation (SEQ ID NO.: 204).